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J Am Chem Soc. Author manuscript; available in PMC 2011 September 8.

Published in final edited form as:
J Am Chem Soc. 2010 September 8; 132(35): 12157–12159. doi:10.1021/ja106989h.

Asymmetric Palladium-Catalyzed Carboamination Reactions for the Synthesis of Enantiomerically Enriched 2-(Arylmethyl)- and 2-(Alkenylmethyl) pyrrolidines

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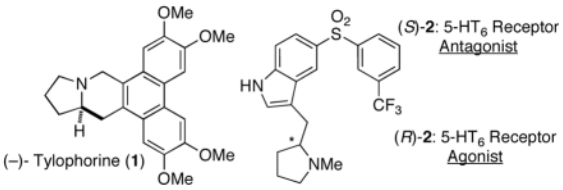
Abstract

The enantioselective synthesis of 2-(arylmethyl)- and 2-(alkenylmethyl)pyrrolidine derivatives via Pd-catalyzed alkene carboamination reactions is described. These transformations generate enantiomerically enriched products with up to 94% ee from readily available alkenyl or aryl bromides and *N*-boc-pent-4-enylamines. The application of this method to a concise asymmetric synthesis of (−)-tylophorine is also discussed.

The *syn*-insertion of alkenes into palladium-nitrogen bonds has been implicated as a key step in a number of important metal-catalyzed processes,[1] including alkene carboaminations,[2] diaminations,[3] and oxidative aminations.[4] In many instances these transformations proceed with high levels of diastereoselectivity. However, enantioselective variants of transformations that involve *syn*-aminopalladation are extremely rare.[5] For example, enantioselective Pd-catalyzed carboamination reactions between aryl/alkenyl halides and alkenes bearing pendant amines have not previously been described, and only two reports of Pd-catalyzed asymmetric diaminations that likely proceed via *syn*-aminopalladation have appeared in the literature.[5]



Over the past several years our group has developed a practical and efficient method for the synthesis of substituted pyrrolidines via Pd-catalyzed carboamination reactions between aryl/alkenyl bromides and γ-aminoalkene derivatives.[1a–b,2] Our success in this endeavor prompted us to investigate an asymmetric variant of these transformations that would generate enantiomerically enriched 2-(arylmethyl)pyrrolidines. These structures are prominent features of many natural products (e.g., (−)-tylophorine, **1**) and pharmaceutical leads (e.g., **2**), and their absolute stereochemistry can have striking effects on biological activity. For example, the *R*-enantiomer of pyrrolidine **2** is a potent 5-HT_6 agonist, whereas the *S*-enantiomer displays antagonistic activity.[6] In this communication we report our preliminary studies on the enantioselective synthesis of 2-(arylmethyl)- or 2-

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(alkenylmethyl)pyrrolidines via asymmetric Pd-catalyzed alkene carboamination reactions.[7,8,9] These reactions proceed with good levels of asymmetric induction, and constitute rare examples of transformations that involve enantioselective *syn*-aminopalladation.

In our initial experiments we examined the coupling of *N*-(boc)-pent-4-enylamine (**3a**) with 2-bromonaphthalene (Table 1). Our prior studies with achiral catalysts indicated that chelating phosphine ligands with relatively large bite angles (e.g., dpe-phos or dppb)[2b] provided satisfactory yields of racemic products. Thus, we examined a series of chiral bis-phosphines for the carboamination of **3a**. Unfortunately, ligands such as (*S*)-BINAP (**5**) or (*S*)-Phanephos (**7**), which possess bite angles similar to dpe-phos and dppb, provided either poor yields of **4a**, low enantioselectivities, or both.[10] We then elected to investigate chiral phosphoramidite ligands for this transformation, as several recent studies have illustrated these ligands are highly effective in other enantioselective Pd-catalyzed addition reactions.[11] Promising results were obtained with BINOL-derived phosphoramidites **8**–**9**, and further exploration led to the discovery that (*R*)-Siphos-PE[12] (**10**) provided useful levels of enantioselectivity. After further optimization of reaction conditions we found that use of 2.5 mol % of $Pd_2(dba)_3$ as precatalyst, a ligand:metal ratio of 1.5:1, and a lower reaction temperature of 90 °C produced **4a** in 78% yield and 82% ee (Table 2, entry 1).

The optimized conditions described above are effective for carboamination reactions between substrates **3a**–**c** and several different aryl or alkenyl bromides. As shown in Table 2, these transformations proceeded in moderate to good yield and provided the desired products with ee's ranging from 72–94%. Although most experiments were conducted on a small scale (0.20 mmol), the coupling of **3a** with 2-bromonaphthalene gave nearly identical results on both small (0.2 mmol) and large (1.0 mmol) scales (entries 1–2). The best enantioselectivities were obtained with β-bromostyrene as the electrophilic coupling partner (entries 12, 13, and 22). Electron-donating groups on the aryl bromide were well tolerated, although this method is less generally effective with electron-poor aryl bromides. For example, reactions of *tert*-butyl *p*-bromobenzoate (entry 10), *p*-bromofluorobenzene (entry 11) and *m*-bromobenzotrifluoride (entries 20–21) proceeded in acceptable yield, but efforts to employ 3-bromobenzonitrile or 4-bromobenzophenone were unsuccessful. Substrate **3b** bearing *gem*-dimethyl substitution at C2 was transformed in similar yields and selectivities as **3a**, although use of a substrate bearing a diethyl acetal at C2 (**3c**) gave a product with lower ee (entry 23). Use of aryl iodide electrophiles gave product yields and enantioselectivities similar to those obtained with aryl bromides. However, aryl chlorides were unreactive under these conditions, and low yields were obtained with aryl triflate substrates due to competing base-mediated cleavage of the sulfonate ester.[13]

In general, side products were not observed in crude reaction mixtures, and it is likely that modest yields result from competing base-mediated substrate decomposition.[2b,14,15] Substrate decomposition was also observed in attempted asymmetric carboamination reactions of substrates bearing 1,1- or 1,2-disubstituted alkenes.

In order to illustrate the utility of the enantioselective carboamination reactions, and to establish the absolute configuration of the pyrrolidine products,[16] a short synthesis of the natural product (−)-tylophorine was undertaken. This molecule exhibits potent antitumor and antiviral activities,[17] and there has been considerable interest in the development of synthetic routes to tylophorine and other related phenanthroindolizidine alkaloids.[7b,18,19]

Our enantioselective synthesis of (−)-tylophorine employs a route analogous to that developed by Herr for the construction of (±)-tylophorine.[18] Aryl bromide **11** was prepared in four steps[18] and then coupled with *N*-boc-pent-4-enylamine (**3a**) using the Pd/(*R*)-Siphos-PE catalyst system (Scheme 1). We were gratified to find this reaction yielded the desired

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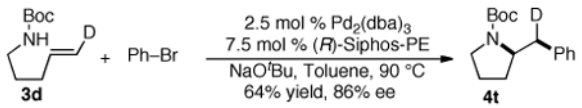
pyrrolidine **12** in 69% yield and 88% ee. Intermediate **12** was converted to (−)-tylophorine (**1**) in two steps[18] and nearly quantitative yield.

The mechanism of Pd/phosphine catalyzed alkene carboamination reactions is believed to involve intramolecular alkene insertion into the Pd–N bond of an intermediate $L_nPd(Ar)(NRR')$ complex (e.g., **13**),[1a,2c] which generates the new C–N bond and forms 1–2 stereocenters depending on the degree of alkene substitution (Scheme 2). Carbon-carbon bond-forming reductive elimination from **14** then leads to generation of pyrrolidine products **4** that result from net suprafacial addition of the aryl group and the nitrogen atom across the alkene.[20] In the enantioselective transformations, it appears reasonably likely that product stereochemistry is determined during the C–N bond-forming step. However, the Siphos-PE ligand has considerably different steric and electronic properties than phosphine ligands such as dpe-phos, dppf, and xantphos, which were employed in the generation of racemic pyrrolidine products.[1a,20] Thus, we sought to determine if the Pd/Siphos-PE-catalyzed reactions also occur with suprafacial selectivity (via a *syn*-aminopalladation pathway). To this end, we examined the coupling of deuterated substrate **3d** with bromobenzene. As shown in equation 1, the pyrrolidine product results from suprafacial addition, which suggests both the asymmetric and non-asymmetric variants of the carboamination reactions proceed through similar mechanisms.



(1)

Although the precise structure of the transition state leading to the major enantiomer is not clear, our data provides some information about the enantiodetermining step of these reactions. The enantioselectivity obtained in the conversion of **3a** to **4a** did not change when ligand:metal ratios were varied from 1:1 to 2:1, which suggests a monoligated palladium complex is involved in the stereochemistry determining step. The poor asymmetric induction obtained with chelating bis-phosphines (e.g., **5**–**7**) may be due to dissociation of one arm of the chelate to provide a four-coordinate complex analogous to **13** prior to aminopalladation. This would place much of the chiral ligand steric bulk at a large distance away from the reactive site, which could diminish asymmetric induction.[21] In contrast, the monodentate phosphoramidite ligands should provide relatively facile access to reactive L_1 complexes. The high selectivities obtained with these ligands may arise from the steric bulk and chiral elements on both the amine group and the diol portion, which appear to be projected around the metal center to a much greater degree than the substituents on ligands such as **5**–**7** when bound through a single P-atom.[22]

In conclusion, we have developed enantioselective Pd-catalyzed alkene carboamination reactions that afford 2-(arylmethyl)- or 2-(alkenylmethyl)pyrrolidines in good yields and enantioselectivities. These transformations provide a new means for the asymmetric construction of this important class of nitrogen heterocycles, and a new route to enantiomerically enriched phenanthroindolizidine alkaloids such as tylophorine. Further studies on the design of more efficient chiral catalysts for these transformations are currently underway.

Supplementary Material

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Acknowledgments

The authors acknowledge the NIH-NIGMS (GM071650) for financial support of this work. Additional unrestricted funding was provided by GlaxoSmithKline, Amgen, and Eli Lilly. The authors thank Dr. Qifei Yang for conducting preliminary experiments in this area.

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11. (a) van den Berg M, Minnaard AJ, Haak RM, Leeman M, Schudde EP, Meetsma A, Feringa BL, de Vries AHM, Maljaars CEP, Willans CE, Hyett D, Boogers JAF, Hubertus HJW, de Vries JG. Adv Synth Catal. 2003; 345:308. (b) Imbos R, Minnaard AJ, Feringa BL. Dalton Trans. 2003:2017–2023. (c) Trost BM, Silverman SM, Stambuli JP. J Am Chem Soc. 2007; 129:12398. [PubMed: 17887679] (d) Yasui Y, Kamisaki H, Takemoto Y. Org Lett. 2008; 10:3303. [PubMed: 18582078] (e) Reddy VJ, Douglas CJ. Org Lett. 2010; 12:952. [PubMed: 20104898]
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13. Efforts to employ weak bases such as Cs_2CO_3 or K_3PO_4 led to low reactivity.
14. Secondary tertbutyl carbamates have been shown to undergo elimination reactions to afford reactive isocyanates when heated in the presence of NaO^tBu. Aqueous workup affords the corresponding primary amines. See: Tom NJ, Simon WM, Frost HN, Ewing M. Tetrahedron Lett. 2004; 45:905.
15. When a solution of **3a** and NaO^tBu (1:1) in toluene*d*8 was heated to 90 °C for 3h ca. 35% decomposition to the corresponding isocyanate was observed. This isocyanate likely is converted to the volatile pent4enylamine upon aqueous workup.

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16. The absolute stereochemistry of **4a–t** was assigned based on analogy to **12**.

17. (a) Zeng W, Chemler SR. Curr Bioact Cmpds. 2009; 5:2. (b) Li Z, Jin Z, Huang R. Synthesis. 2001:2365.

18. A recent syntheses of racemic tylophorine was reported that employed a Pdcatalyzed alkene carboamination reaction between **3a** and **11** to generate the heterocyclic ring. See: Rossiter LM, Slater ML, Giessert RE, Sakwa SA, Herr RJ. J Org Chem. 2009; 74:9554. [PubMed: 19919084]

19. For selected recent syntheses, see: (a) Fürstner A, Kennedy JWJ. Chem Eur J. 2006; 12:7398. (b) McIver A, Young DD, Dieters A. Chem Commun. 2008:4750. (c) Wang Z, Li Z, Wang K, Wang Q. Eur J Org Chem. 2010:292. and references cited therein.

20. Studies on the reactivity of (dppf)Pd(Ar)[N(Ar)$(CH_2)_3CH{=}CH_2$) complexes indicate that the rates of aminopalladation and reductive elimination are comparable, and that aminopalladation is not reversible under the conditions of the stoichiometric reactions. See: Neukom JD, Perch NS, Wolfe JP. J Am Chem Soc. 2010; 132:6276. [PubMed: 20397666]

21. A related hypothesis has previously been invoked to account for the effect of reaction conditions on asymmetric induction in enantioselective intramolecular Heck reactions. See: Dounay AB, Overman LE. Chem Rev. 2003; 103:2945. and references cited therein. [PubMed: 12914487]

22. No Xray structural data for palladium complexes of **10** has been reported in the literature. However, this is evident in xray data reported for a allylpalladium complex bearing a single chiral phosphoramidite ligand derived from BINOL and bis(1phenylethyl)amine. See: Mikhel IS, Rüegger H, Butti P, Camponovo F, Huber D, Mezzetti A. Organometallics. 2008; 27:2937.

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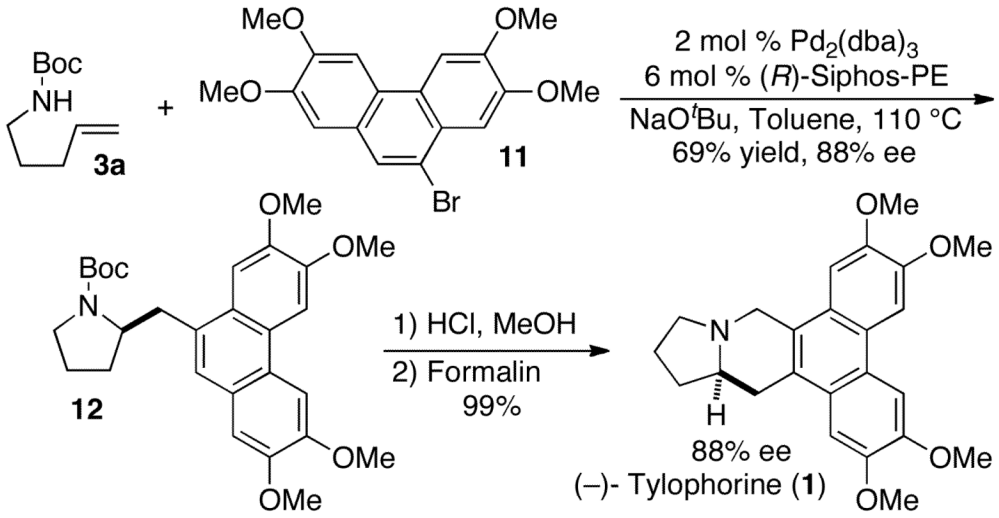

Scheme 1.
Synthesis of (−)-Tylophorine

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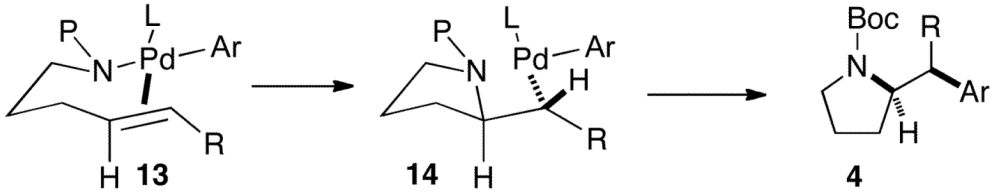

Scheme 2.
Syn-Aminopalladation Mechanism

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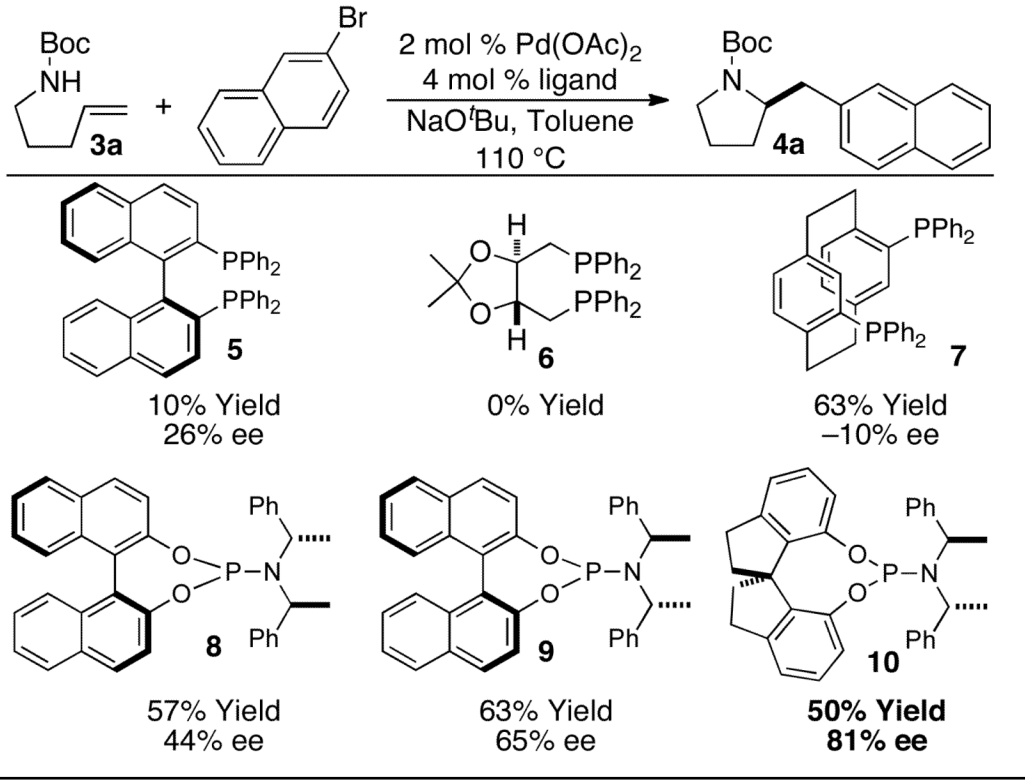
Table 1

Chiral Ligand Screen[a]



[a]Conditions: Reactions were conducted on a 0.15 mmol scale with 1.0 equiv substrate, 1.2 equiv ArBr, 1.2 equiv NaO^{t}Bu, 2 mol % $Pd(OAc)_2$, 4 mol % ligand, toluene (0.15 M), 110 °C, 14 h.

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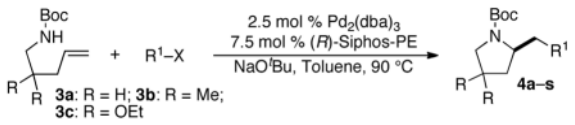
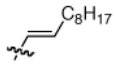
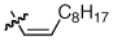
Table 2

Catalytic Asymmetric Synthesis of Pyrrolidines[a]



Entry	R	R^1	X	Product	ee[b]	Yield[c]
1	H	2-naphthyl	Br	**4a**	82%	78%
2	H	2-naphthyl	Br	**4a**	82%	75%[d]
3	H	C_6H_4-*o*-Me	Br	**4b**	84%	75%
4	H	C_6H_4-*o*-Me	I	**4b**	85%	74%
5	H	C_6H_4-*m*-OMe	Br	**4c**	87%	73%
6	H	C_6H_4-*p*-OMe	Br	**4d**	86%	72%
7	H	C_6H_4-*p*-OMe	I	**4d**	86%	70%
8	H	C_6H_4-*p*-OTBS	Br	**4e**	90%	64%
9	H	C_6H_4-*p*-CH_2OTBS	Br	**4f**	85%	68%
10	H	C_6H_4-*p*-$CO_2{}^t$Bu	Br	**4g**	72%	61%
11	H	C_6H_4-*p*-F	Br	**4h**	80%	66%
12	H	(*E*)-β-styryl	Br	**4i**	93%	76%
13	H	(*Z*)-β-styryl	Br	**4j**	94%	61%
14	H		Br	**4k**	82%	61%
15	H		Br	**4l**	91%	62%
16	Me	2-naphthyl	Br	**4m**	88%	80%
17	Me	C_6H_4-*p*-(^{t}Bu)	Br	**4n**	82%	80%
18	Me	C_6H_4-*p*-OMe	Br	**4o**	85%	69%
19	Me	C_6H_4-*p*-NMe_2	Br	**4p**	92%	70%
20	Me	C_6H_4-*m*-CF_3	Br	**4q**	91%	70%
21	Me	C_6H_4-*m*-CF_3	I	**4q**	91%	71%
22	Me	(*E*)-β-styryl	Br	**4r**	93%	70%

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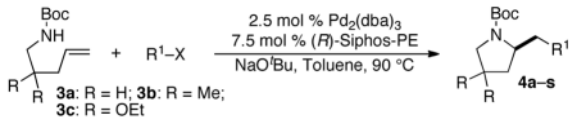

Entry	R	R^1	X	Product	ee[b]	Yield[c]
23	OEt	C_6H_4-*p*-Ph	Br	**4s**	75%	64%

[a]Conditions: Reactions were conducted on a 0.2 mmol scale with 1.0 equiv substrate, 2.0 equiv ArBr or alkenylBr, 1.0–2.0 equiv NaO^{t}Bu, 2.5 mol % $Pd_2(dba)_3$, 7.5 mol % (*R*)-Siphos-PE, toluene (0.2 M), 90 °C, 12–15 h.

[b]Enantiomeric excess was determined by chiral HPLC analysis.

[c]Isolated yield (average of two or more experiments).

[d]This reaction was conducted on a 1.0 mmol scale.